Phytotherapy as alternative to hormone replacement therapy

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1. ABSTRACT

Phytoestrogens are a group of non-steroidal compounds of plant origin that present structural and functional similarities with estradiol. Isoflavones are their most widely known category. There are different mechanisms of action of isoflavones accepted, although they may be considered as selective modulators of estrogen receptors. On the other hand, *Cimicifuga Racemosa* is a perennial plant used traditionally for problems related to menstruation. Its action mechanisms have not been totally identified. There is a growing interest in the usefulness of phytotherapy in the treatment of symptoms and menopause-related diseases. Isoflavones and *Cimicifuga Racemosa* moderately improve vasomotor symptoms in menopausal women, particularly in those who have a greater number of hot flushes. Furthermore, trials performed with soy isoflavones have observed a reduction of the loss of bone mineral density in postmenopausal women and a slight decrease in LDL cholesterol. In short, phytotherapy will constitute a therapeutic option that can offer assistance to women who want to improve their quality of life through relief of vasomotor symptoms or benefit from other effects for their health.

2. INTRODUCTION

From the prevalence data obtained of symptoms associated with menopause, the vasomotors (hot flushes) are the most frequently reported by women. They are experienced by more than 50% of them, and may persist years after the cessation of menstruation, subsequently affecting the quality of life. In a systematic review of these symptoms, a frequency of 30-50% of host flushes was estimated in perimenopause and 30-80% in the postmenopause, with a duration of one year for 80% of the women and persistence at the age of 60 in 12-15% of them (1).

Substitutive hormone therapy has demonstrated to be effective in the treatment of these vasomotor symptoms (2). However, treatment follow-up rates are low, as many women never start and others withdraw early, because of factors such as: the perception that menopause and its disorders are a natural fact, fear of possible side effects like cancer or uncertainty regarding pharmacological manipulation. To all this it should be added the effects of media coverage of the WHI study (Women's Health Initiative) and the messages of some health authorities.

Therefore, phytotherapy has gained support, has a greater demand and is better received by the perception that natural products are better and, thus, more safe and without side effects, what obviously is not quite correct. Thus, a growing acceptance of its use by women has been found, although not as an alternative to classical medicine or as incompatible with the use of medicines, but within an inclusive attitude of the different types of treatments for their healthcare. This greater demand has also led to an increasing number of professionals who are more and more interested in phytotherapy and who prescribe products based on medicinal plants. In fact, it is estimated that an 80% of gynecologists prescribe them to their patients.

Another important aspect is the information women receive from primary care physicians, gynaecologists, drugstores, herbalists, written press, relatives, friends, or health authorities. These informations are often so divergent that lead women to confusion.

In any case, there is a growing interest in Western countries in the usefulness of phytotherapy in the treatment of symptoms and menopause-related diseases and ageing, which has resulted in the appearance of a significant number of publications that sometimes present conflicting results.

To the question raised on what are the limits of phytotherapy it could be answered that these will be the limits of the evidence. In this sense, the Spanish Menopause Society (SMS) has held two positions statements about isoflavones and *Cimicifuga Racemosa* with the aim of defining the standards of a good clinical practice (3, 4). Therefore, a multidisciplinary group of clinicians and researchers in the field of phytotherapy has performed the analysis of the best evidence available in this field to develop some documents based on them on the role of isoflavones and *Cimicifuga Racemosa* in the health of menopausal women.

3. ISOFLAVONES

3.1. General characteristics

Phytoestrogens are a large group of non-steroidal compounds of plant origin that present structural and functional similarities with estradiol. According to its chemical structure they are classified in four different groups: isoflavones, stilbenes, lignans and coumestans. Isoflavones are the most widely known and studied category. They are found in a great variety of plants, mainly in legumes such as soy and red clover, and mostly linked to glucides which after hydrolysis give rise to free forms or aglycones. The most important and widely known aglycones are genistein, daidzein, glycitein, biochanin A and formononetin.

Initially, the interest in isoflavones derived from the observation in the 90's that Japanese women consuming a traditional diet with a large amount of soy had lower incidence of hot flushes, breast cancer, cardiovascular disease, and osteoporosis and climacteric symptoms (5). For this reason, Western women have increased their daily intake of soy with the hopes of also obtaining the beneficial effect of the traditional Japanese diet in health. Many studies have examined the effect of soy and its components in the incidence and severity of hot flushes in peri- and postmenopause, using soy protein or isoflavones derived from soy or red clover.

3.2. Difficulties in research

There following difficulties are identified when analyzing and unifying the results of the studies on the effects of isoflavones in menopausal women: the wide range of preparations used, the different size of samples, the different duration of the studies and the great variability in the doses used (6). Quantification of isoflavones in the diet is complicated due to the wide variability of the concentration and composition of these in the different soy foods, soy protein products, supplements or other sources. Furthermore, differences in the growing region, climate, storage method or manufacturing may have different effects on the final product. Moreover, individual factors such as individual bioavailability, the action of intestinal bacteria and antibiotics, idiosyncratic capacity to produce equol by intestinal metabolization of daidzein (with the most potent antioxidant activity and only present in 30% of the population) or the exposure time and the timing thereof, are also important in the resulting effect. All this, explains the variations and discrepancies that lead to the inconclusive and contradictory results of the studies (7, 8, 9).

3.3. Mechanism of action

According to last knowledge, there are several action mechanisms of the isoflavones nowadays accepted. Despite its structure does not derivate from steroid nucleus, its space disposition and the distance between two of its hydroxyl groups is similar to 17-beta-estradiol. These isoflavones structural characteristics justify its union capacity with estrogenic receptors (ER) (19), with a higher affinity, especially genistein, with beta-ER (1/3 of those of 17-beta-estradiol) than with alpha-ER. That means, due to the different tissue distribution of both ER, which its effects may be tissue-selective considered.

Genistein is able to increase the union of beta-ER to the estrogenic response element and to recruit co-activators for the beta-ER and not for alpha-ER, which has as a consequence an increase in its transcriptional activity (11). These fact determine that isoflavones, and genistein in particular, are considered as selective modulators of estrogenic receptors. Besides its preferential union with nuclear beta-ER, isoflavones join to membrane receptors, implicated in quick response to estrogenic agonists (12, 13).

With concentrations ten times higher than needed to interact with estrogenic receptors, they act over other nuclear non estrogenic receptors named PPAR (Peroxisome Proliferator Activated Receptors), in particular with PPAR-gamma, implicated in processes such osteogenesis, adipogenesis, cell proliferation and apoptosis (14). Moreover, they have antioxidant activity with positive repercussions in lipoproteins oxidation degree and the

atheroma plaque formation (15). In addition, they have showed inhibitory activity over hormonal metabolism enzymes, in the beginning and development of cancer, in inflammatory mediators production and in cholesterol metabolism (16). Finally, they have showed other actions as the increase in nitric oxide production, the decrease in intracellular calcium, the increase of vasodilator response to acetylcholine and the inhibition of thromboxane A_2 union to its platelet receptor. All together indicates that the joint of these actions, even the discreet ones, may confer them a wide pharmacologic activity profile (3).

3.4. Vasomotor symptoms

Of the randomized placebo-controlled studies that have addressed this aspect, the first conclusion that is worth mentioning is that isoflavones moderately improve vasomotor symptoms in menopausal women, particularly in those who have a greater number of hot flushes (17, 18, 19). Nevertheless, the comprehensive assessment of these results points out the inconsistency of the effect, probably due to the differences among the studies in aspects such as dose, period of use and type of preparation used. Most of the researches have used isoflavones derived from soy, and fewer isoflavones from red clover.

The various systemic reviews of these placebo-controlled studies have not shown homogeneous results. In a review of eleven randomized studies, three of them showed a positive effect, lasting at least 6 weeks (20). In addition, three other reviews, one including 2,348 women, found no improvement in vasomotor symptoms or the results were contradictory or inconclusive. In one of them, isoflavones derived from red clover (6, 9, 21).

A Cochrane review published in 2007 highlighted the difficulties involved in phytotherapy research and the limitations to draw conclusions. To this regard, the review noted the wide variability of the placebo effect (from 1-59%), the variations in the source of isoflavones (dietary soy, red clover, soy extracts), the different doses used, the variable times of analysis and the lack of unanimity in the assessment of symptoms. As a result, it indicates the impossibility to obtain evidence to recommend the use of phytoestrogens as treatment of vasomotor symptoms (22). Following this trend, in a recent review of 23 studies, 17 of them with soy isoflavones and 6 with red clover, no conclusive evidence was found of the benefit of the treatment with isoflavones, and only indicated some benefit from soy isoflavones (23).

A metaanalysis that included 6 clinical trials that assessed the frequency and severity of the symptoms found no effect when the source of isoflavones was red clover, whereas with soy isoflavones a limited but statistically significant effect over placebo was observed (24).

Another meta-analysis of 17 randomized trials with at least 4 weeks of treatment, chosen for showing the change in the number of hot flushed per day, observed that the effect of soy isoflavones on the frequency of hot flushed was clinically modest but statistically significant, noting also that this effect appeared to be related with the frequency of hot flushes and possibly with the doses used (19).

A review of 11 placebo-controlled trials that had used soy extracts of known composition in terms of quantity and type of isoflavones found that when preparations contained 15 or more mg/day of genistein, the decrease of the number of hot flushes was statistically significant compared to the control group (25). In turn, a systematic review and subsequent meta-analysis of 5 studies on the effect of red clover in relieving the symptoms showed a decrease of 1.5 hot flushes per day in the treatment group in comparison with the placebo group (26).

Regarding the positioning of scientific societies, the North American Menopause Society consensus document of 2000 concluded that hot flushes decreased only slightly in women consuming soy-derived isoflavones when comparing them with control groups. Likewise, it pointed out the difficulty of comparing studies due to the different products and dosages used and the variation in assessment rates of clinical efficacy. In any case, it recommended using doses between 40-80mg/day (27). Subsequently, in its positioning of 2004, the document pointed out that the measure of effectiveness in clinical trials, both for those assessing diets rich in soy and the extracts of soy and red clover, showed results that were not homogenous, possibly related with the status of many women as producers of metabolite of daidzein, which has a higher estrogenic potency. Thus, it concluded that isoflavones should be recommended for women with symptoms at doses of 40-80 mg/day and pointed out that the effect, in case it appear, it can take several weeks to manifest. It also indicated the low incidence of side effects of these substances, but recommended caution *in* situations in which the estrogenic effect may be dangerous, such as in women with history of breast cancer (28).

For its part, the position of SMS concluded that the available evidence highlighted that isoflavones improved vasomotor symptoms moderately, particularly in those women with higher number of hot flushes. It was suggested doses between 40-80 mg/day as the adequate, with a minimum content of 15 mg of genistein (3).

3.5. Isoflavones and bones

Most clinical trials performed with soy isoflavones to investigate their impact on bone mass have observed a reduction of the loss of bone mineral density (BMD) in postmenopausal women. This effect occurs early, even with early onset at 6 months and which may stay up to 2 years. Several studies have shown a positive effect, with follow-up between 6 and 12 months, using as study variables BMD and biochemical markers of bone remodeling. These studies show a beneficial effect on postmenopausal bone loss with an increase of bone mass or decrease of its loss, assessed by BMD and remodeling markers, with a decrease in bone resorption markers (more common) and increase or absence in bone formation markers (29, 30).

Especially interesting is the randomized double-blind placebo and hormonal therapy (HT) controlled clinical trial of Morabito in 2002. This trial studied the effect of genistein on bone metabolism and BMD, noting that genistein (54 mg/day) and HT (1 mg of estradiol associated with 0.5 mg of norethindrone) resulted in increased BMD at the femoral neck (genistein 3.6 ± 3%, HT 2.4 ± 2% and placebo -0.65 ± 0.1%; p > 0.001) and the lumbar spine (genistein 3 ± 2%, HT 3.8 ± 2..7% and placebo –1.6 ± 0.3%). The study also noted after 1 year follow-up, both a statistically significant difference of genistein versus placebo and parallelism between genistein and HT (31).

In turn, in 2007, Marini, administered placebo or 54 mg/day of genistein (both with calcium and vitamin D) in a randomized double-blind placebo-controlled trial to 389 menopausal women with densitometric osteopenia in femur neck during 24 months. The results of this study showed a decreased BMD in lumbar spine in the placebo group, and an increase of the same in the genistein group both in the lumbar spine (difference of 0.10 g/cm^2 [CI: 0.08-0.12]; p < 0.001) and the femur neck (difference of 0.062 g/cm^2 [CI: 0-0.073]; p < 0.001), concluding that genistein during 24 months showed a positive effect on bone mass in postmenopausal osteopenic women (32).

In a review of 31 studies performed in 2006 on the effects of phytoestrogens in postmenopausal women, of which only 6 met inclusion criteria (three used pure compounds or soy extracts and other three foods containing soy protein or SPI), changes in BMD and bone remodeling markers were assessed. The results obtained suggested that phytoestrogens of the sources used showed a beneficial effect on bone health (33).

A recent meta-analysis, in which ten clinical trials with a total of 608 women have been reviewed, indicated that isoflavone intervention can significantly contribute to increased BMD or reduced bone loss in column, especially in postmenopausal women and with isoflavone intake of more than 90 mg/day, consumption during 6 months may be sufficient to achieve these favorable effects (34).

In short, current clinical data suggest that soy-derived isoflavones, either in extracts and dietary intervention, can reduce or avoid postmenopausal bone loss evaluated densitometrically and by markers of bone metabolism and, therefore, reduce the risk of osteoporosis.

So far only one epidemiological cohort study has been published in which the association between dietary soy intake and the risk of bone fractures has been analyzed. This study has shown an inverse relationship between soy food consumption and the rate of bone fractures (35).

For its part, SMS has suggested some beneficial effect on postmenopausal bone loss (assessed by BDM and bone remodeling markers) (3).

3.6. Cardiovascular system
Regarding the benefits of isoflavones on the cardiovascular system, there are different aspects that can be highlighted according to the evidence available. First, a slight decrease of plasma concentrations of LDL cholesterol in several meta-analyses has been demonstrated, especially in patients with history or previous hypercholesterolemia (36, 37, 38). Similarly, some antioxidant (39) and favorable actions has been observed on several cardiovascular risk parameters such as insulinemia and insulin resistance among others, without observing any deleterious effect on coagulation (40).

Moreover, there are also some encouraging data on endothelial function, although so far not conclusive. In this sense, the treatment with isoflavones has been associated, regarding reactivity of the brachial artery, with improved endothelium-dependent vasodilatation and decrease of endothelial adhesion molecules ICAM1, VCAM1 and E-Selectin, which suggest a positive effect of isoflavones on endothelial function (41).

SMS concluded that there is evidence of a slight decrease in LDL cholesterol concentration, especially in hypercholesterolemic patients, as well as an antioxidant action and a favorable action on cardiovascular risk parameters without adverse effects on coagulation (3).

3.7. Effects on breast
The relationship between dietary phytoestrogens and breast cancer has been evaluated in several studies and reviews in recent years. One of the last, published in 2006, analyzed 19 epidemiological studies and 10 case-controls studies using dietary questionnaires, and concluded that there are no clear evidences on the fact that the intake of isoflavones in the diet influences the incidence of breast cancer, thus there is no evidence to indicate a high consumption to prevent the occurrence of said disease (42).

Another meta-analysis performed the same year assessed the relationship between exposure to soy and breast cancer by analyzing 18 epidemiological studies (12 case-controls and 6 cohorts). By a combined analysis of all the included patients it was concluded that high soy intake was modestly associated with reduced risk of breast cancer (OR 0.86; CI 95%: 0.75-0.99). When the analysis was performed according to menopausal status, this association was stronger in premenopausal women (OR 0.70; CI95%: 0.58-0.85). Furthermore, when analyzing the consumption of soy protein in grams the association was only found during premenopause. However, these results should be interpreted with caution because of poor exposure classification, existence of confounding factors and lack of dose-response results (43).

Other studies have attempted to assess the relationship between breast parenchymal density pattern by mammography, which has proved to have positive predictive value for the occurrence of cancer, and soy intake. One of them studied 406 women between 41 and 74 years old and found that high soy intake, assessed by dietary questionnaires from the previous 12 months, was inversely related to risk or high risk parenchymal pattern (OR 0.42; CI95%: 0.18-0.94). The conclusions drawn was that high intake of dietary soy could have important

implications in preventing breast cancer, although it should be taken into account that the study was conducted with Chinese women consumers of large amounts of soy in childhood and adolescence (39). Conversely, another study of Japanese, Chinese and Caucasian women in Hawaii found a different effect, noting that soy intake and breast density were positively related (45).

SMS concluded that there is no evidence on the fact that phytoestrogen administration in postmenopause reduces the risk of breast cancer, although some studies may suggest some protection during postmenopause. Therefore, there is no data available to justify the use of phytoestrogens in preventing cancer or recurrence in women with history of breast cancer, and there are no data that suggest that eating soy-rich foods has adverse effects on breast in healthy population (3).

3.8. Action on the endometrium
Several studies have assessed endometrial safety associated with phytoestrogen consumption. Although the follow-up period in these studies ranges from 12 weeks to 5 years, most of them have been developed during 6-12 months, with doses ranging from 36-100 mg/day, except for one study that used a dose of 150 mg/day. The control methods used were transvaginal ultrasound, Doppler ultrasound, endometrial histology and hysteroscopy. Only the study that administered a dose of 150 mg/day of phytoestrogens and had a follow-up of 5 years, found an increase of simple endometrial hyperplasia in the treatment group in comparison with the placebo group (46).

In conclusion, regarding the effect of phytoestrogen consumption on the endometrium with the evidence available, it can be concluded that no adverse effects have been found at the recommended doses (40-80 mg/day), and that there is not enough evidence on long-term endometrial safety with high-doses (3). For this reason, most studies highlight the need to provide information to patients about the doses that seem to be more secure and the caution to avoid overdosage.

3.9. Other actions of isoflavones
Besides the above, other actions of isoflavones have been studied. Regarding vaginal trophism, there are insufficient data to assess its effect on the epithelium, and with the limited data available they do not seem to have significant effects. Moreover, the local application of phytoestrogens on the skin seems to reduce the effects of skin aging, although the value and extent of this effect is still unknown. Finally, with regard to cognitive function there are few clinical trials, although it can be deduced from them some positive effects in women with recent menopause, especially concerning the memory.

3.10. Developing researches
Currently, several studies are being conducted on the effect of isoflavones in different areas of human health. From these studies, 13 clinical trials can be highlighted, all of them in phase I, II or III, randomized, double-blind and placebo-controlled with crossover or parallel assignation. Most of these studies are, which are in progress, have been designed to assess the effect of isoflavones on bone

remodeling and bone mass markers, breast density, breast cancer prevention and cognitive function (47).

4. CIMICIFUGA RACEMOSA

4.1. Generalization
Cimicifuga racemosa (CR) is a perennial plant originated in North America that was used traditionally by the American Indian for "women problems", specially related to menstruation and birth. Lately it took part of the composition of the best seller product in the United States during XIX century, Lidia Pinkham's women's tonic, which stirred interest as a treatment of the climacteric symptomatology. It's also been used in Germany in the 40's to relieve vasomotor symptoms.

In the CR multiple molecules have been identified but its exact action mechanism related to vasomotor symptomatology has not been clearly stated. Its roots and rhizomes present a complex composition, being its most distinctive composites triterpenic glycosides derived from the cyclo artanol nucleus, which main representative are actein, 27-epi-deoxi-actein, the cimirracemosides and cimicifugoside; and the phenolic derivatives, represented basically by cafeic acid esters, like the fukinolic acid. Other phenolic derivatives, like the formononetine, have been found as traces, without clinical significance.

4.2. Action mechanisms
Action mechanisms of CR have not been totally identified, even though nowadays knowledge allow ruling out the interaction with estrogenic receptors alpha and beta and with those of progesterone and androgens (48). It's possible the existence of several action mechanism and hence different effects. At present, research is focused in the possibility of action over different neurotransmission systems related to a greater or lesser degree with corporal temperature changes (49, 50).

Mechanisms involved in the effect over vasomotor reaction seem to be associated with the interaction with different neurotransmission systems, like D2 dopaminergic receptors (51), 5-HT1A serotoninergic (52) and mu opioid receptors (50). Adrenergic system is also directly involved in the maintenance of corporal temperature and has been communicated that cimicifugoside may inhibit the chatecolamines secretion mediated by stimulating the acetylcholine nicotinic receptors (53). Furthermore, the complexity of composition and action of such composites suggest the possibility of other positive actions in other locations.

The possible effect over bone remodelling is supported in researches made *in vitro* with components of the CR, like the cimicifugoside, that showed an action over the osteoclastogenesis due to the inhibition of cytokines (RANKL y TNF-alpha) (54) and an increasing in the production of osteoprotegerine (49). All of that may contribute to a better balance of bone remodelling.

In relation with its possible effect in preventing carcinogenesis or in favourable effects over tumours, both triterpenic and phenolic derivatives have shown *in vitro* actions over cancer cell lines at different levels, as DNA replication or apoptosis inductors activation (55). Inhibition of certain enzymes (sulfotransferases, collagenase, and 5-alfa-reductase) may be involved in this question and the ACTH secretion may explain a higher resistance to stress (56).

4.3. Vasomotor symptoms

Several randomized researches, with periods of treatment between 12 weeks and 1 year and with a number of patients between 62 and 351, have proved a CR effect higher than placebo in the control of vasomotor symptoms. Among them, just one research (57) found a benefit in cases with severe symptomatology (Kupperman index ≥ 25). In an opposite way, the results from Herbal Alternatives for Menopausal Trial (HALT study), that included 351 symptomatic peri and postmenopausal women, randomized in 5 possible groups of treatment: CR alone (160 mg/day), a multibotanical formulation (200 mg CR plus other 9 ingredients), a multibotanical formulation plus a phone call recommending dietetic soy consume, conjugated equine estrogens (0, 625 mg) with or without progesterone and placebo didn't found a significant reduction in frequency and severity of the vasomotor symptoms with CR (58).

Other researches have compared directly the effects of the CR with estrogenic formulations. In a randomized double blind assay with 62 menopausal symptomatic women, it was compared the efficacy of 40 mg/day of CR with 0.625 mg/day of conjugated equine estrogens or placebo, using the Menopause Rating Scale (MRS), and showing an efficacy of the CR over the stifles higher than placebo (statistically significant) and similar to those with estrogens (59). In this way, Nappi researched the CR efficacy 40 mg/day against transdermic estradiol 25 mcg/day, finding a similar reduction in the number of stifles in both groups (60).

A recent multicentric randomized and double blind research in 244 menopausal women has analyzed the efficacy and security of CR against tibolone (40 mg/day against 2.5 mg/day). The results showed a clinical improvement similar in both groups, as well as a similar response percentage (84% and 85%), being superior the CR in its security profile (61).

Related to women with breast cancer and vasomotor symptoms, with the premise that CR hasn't estrogenic action, it has been suggested that it may be used in such women, treated or not with tamoxifen. Nevertheless, the results of three researches in that sense have shown no conclusive data relating to efficacy (62, 63, 64).

Finally, there's no meta-analysis evaluating efficacy of CR in the vasomotor symptoms treatment. In relation of what different scientific societies state, the American College of Obstetrician and Gynaecologist affirmed in 2001 that CR may be helpful used during a short time (less than 6 months) in the treatment of women with vasomotor symptoms (65). NAMS in its Position Statement of 2004 concluded that in recent researches the results had been negative, but, however, old small german researches had shown some efficacy in treating the stifles. This way, with the low incidence of secondary effects, supplementation with CR (2 tablets 20 mg/day) during less than 6 month may improve mild stifles (28).

SMS concluded recently that beneficial effects of CR have been shown in the vasomotor symptoms relieve, with more effect in those women with severe symptoms. Recommended and more studied dose is 40 mg/day in 2 times (4).

4.4. Effects on mood

Most of the researches about CR have been focused over menopausal symptoms. However, in some of them there's a comment about its actions on mood. Several researches, prospective, observational, not controlled, have found that with 40 mg/day f CR a significant improvement in mood would be achieved, as well as less nervousness, insomnia and irritability. Even more, with CR monotherapy or associated with 0.25 mg hypericum has shown an improvement on mood in both groups, but higher with the association of both substances (66, 67, 68).

It's to consider a prospective research, double blind and controlled with placebo, that in 2005 evaluated the treatment with 40 mg/day CR during 12 weeks in the psychic sphere in 304 women, being CR more effective than placebo in function of time between symptoms beginning and FSH levels. Women more benefited from treatment were those in a early climacteric phase, whose MRS scale global grading improved and specially "Psique" subscale in a significant way respecting to placebo (69). Nappi *et al.* research compared as well the effect of 40 mg/day CR against transdermic estradiol in a low dose, showing a significant improvement in depressive symptoms and anxiety 3 months after with both treatments, with no differences between them (60).

Finally, a recent prospective research, open, observational has analyzed the impact of CR in the quality of life in 122 symptomatic menopausal women using as evaluating method the Cervantes scale of quality of life. It showed an improvement in the global punctuation in the quality of life of these women, describing a higher improvement in menopause and health domain in 50-54 years old group, in psychic domain in 45-49 years old group and in sexuality and pair relationship in 55-59 years old group (70).

SMS concludes that there are no specific researches to evaluate the effects of CR over psychic symptoms and mood, although many of the observational researches and clinical assays show a benefit in symptomatic menopausal women (4).

4.5. Effects on cancer

Knowing the potential action mechanisms described for CR, the relation between its use and

carcinogenesis or the effects it may have in patients with neoplasias are relevant beyond its possible use over symptoms in cancer patients.

According to its relation with breast cancer carcinogenesis, *in vivo* researches with normal mammarian tissue hasn't showed no estrogenic effects of the CR extract from the cytological point of view, over the protein induced by estradiol pS2 expression or over Ki-67 expression (cell proliferation marker) (71,72). Furthermore, it's been observed the local estrogen synthesis inhibition in mammarian tissue in pre and post menopausal patients (73).

Over breast cancer cells, *in vitro* researches have shown an absence of proliferative effects of CR extracts over MCF-7 cells and the inhibition of cell growth, not only of MCF-7 cells (ER+) but also of MDA-MB-453 cells (ER-, Her+) (74,75).

On the other side, it's been described that actein inhibits the capacity of forming colonies of MDA-MB-453 cells and of modelling the expression of several genes in MCF-7 cells, favouring cell apoptosis and reducing DNA replication and cell cycle progression (55). Furthermore, it's been communicated that the CR etanolic extract is able to inhibit the estradiol synthesis from oestrone sulphate, probably by the selective action over sulphatase enzyme (76). Other effect of the CR extracts over human breast cancer cells ER+ are its estrogenic antagonist action and its antioxidant and anti free radicals action (77, 78).

The ability to induce human breast cancer cells apoptosis have been described in ER+ as well as in ER- (79, 80). Furthermore, CR has also proved the ability to inhibit the growth of human prostate cancer cells LNCaP and to counteract the estradiol or dehydrotestosterone proliferative effect (81), as well as to inhibit carcinogenesis *in vivo* in mice skin (82).   Other relevant aspect is the possible interaction of CR with complementary cancer treatments. *In vitro* researches over MDA-MB-453 cells, actein and etilacetate fraction of CR extract showed synergic effects with paclitaxel and doxorubicin (83). Another research with EMT-6 breast cancer mice cells pointed out interaction of CR with different agents used in the cancer treatment, positive for doxorubicin and docetaxel, neutral for 4-HC (a cyclophosphamide analogue) and radiotherapy and negative for cysplatinum (84). Finally, another research has proved synergic effects with tamoxiphen over MCF-7 human breast cancer cells (85).

However, there are few clinical researches about the CR treatment in cancer patients. Rebbeck did a retrospective case/control research about the association between different supplements use, including CR extracts, and the relative risk of suffering breast cancer, showing a risk reduction between CR consumers (OR:0.39, 0.22-0.70) (86). In this way, in another cohort research in 18.861 patients showed a extension of disease free interval and a reduction in the recurrence rate in the patients consumers of CR against not consumers, with a hazard ratio of 0.83 (IC 0,69-0,99) (87).

SMS, in its position statement document conclusions, points out that several experimental researches agree in the findings of some potentially beneficial effects in carcinogenesis prevention and/or certain cancers treatment, even when no clinical assays guarantee such possibility. With the data we know, it's possible to conclude that CR formulations aren't a risk for cancer patients. Some of the clinical assays affirm that it could have even beneficial actions over the disease evolution. However, more randomized clinical assays are needed to confirm experimental data before establishing definitive conclusions, including not only aspects relative to disease evolution but also those related to interactions with therapeutical measures normally used (4).

4.6. Other actions of cimicifuga racemosa

There are few researches specifically dedicated to evaluate the effect of CR over other parameters than the above mentioned, even they have been treated as secondary variables in many of the researches publicated.

There is no scientific evidence that suggests any action of CR over vaginal epithelium or endometrium. In some researches a little increase in the number of superficial vaginal epithelium cells has been described, which may improve vaginal dryness. In this way, it's been proved that CR wouldn't act over estrogen regulated genes expression in such tissues (88, 89, 90). It's not been observed clinical significant changes in lipidic profile, even some results inform about a seric increment of triglycerides, a possible cholesterol HDL fraction increase and a decrease of LDL fraction. No increment in cardiovascular adverse effects has been found. Finally, even there are some positive results in bone formation, these come from experimental researches, with no specific researches about bone mass (4).

4.7. Side effects of Cimicifuga Racemosa

From the revision of drug security researches it can be assumed that treatment with CR, in any of its presentations or dosages, presents a good security profile. This affirmation is more true the modern the CR formulation used is, so it's important to distinguish the security in present formulations, specially isopropanolic formulations, from the observed with old formulations or with less purity (91). A recent revision of 13 clinical assays, referring to security, 3 post commercialization security researches, four cases series and 8 publications of isolated clinical cases concluded that CR treatment was secure (92). In fact, evaluating last 10 years publications, where another methodological requirements in investigation and in medical literature are considered, frequency of relevant secondary effects is very low and in slight most cases, self-limited and with no need to interrupt the treatment (93). A German commission that watch over the phytotherapic products security hasn't identified CR interactions with no other drug used in dysmenorrhoea, premenstrual syndrome or climacteric disruptions treatment (94).

According to the dose used, Liske in 2002 compared 2 groups of patients with high dose (127.3

mg/day) or standard dose (39 mg/day) administration, with no higher adverse effects in those with high dose treatment (95).

In the last years it's been communicated some cases of severe hepatic affection in patients that had taken CR formulations as treatment for vasomotor post menopausal symptoms. Severity and evolution to fulminant hepatic failure in some of them alerted sanitary authorities and motivated that European Medicines Agency (EMEA) published in July 2006 a release that warned of its possible relation, waiting for a deeper analysis of the topic (96). According to that, Lude researched in 2007 the possible hepatotoxicity of alcoholic extracts in CR in an *in vivo* experimental mice model and proved that the extract caused microvesicular fatty liver disease, just with high dose. They used some *in vitro* experimental models showing that's due to an apoptosis stimulus and not for hepatocyte necrosis. Comparing toxic doses which those used in women stifles symptoms, the authors affirmed that the mitochondrial beta-oxidation began with 3-5 higher doses and the relevant toxicity with 30-150 higher doses than those used in clinic. So, they concluded that its findings were not clinically relevant and that, anyway, it may be in certain patients, due to their idiosyncrasy or to risk underlying conditions not well known (97).

In any case, despite the clinical cases of autoimmune hepatitis, fulminant liver failure and toxic hepatitis related to CR extracts dose, the pharmacologic use of such drugs extends over more than 60 years estimating the use of more than 350 million doses from the pharmacovigilance implantation without suspecting this relation (98). EMEA itself, in the detailed analysis of the communicated cases, describes that most of them are few documented, were in polimedicated women or using uncertain composition formulations, which suggests that it's not probably the casual relation and, in any case, this adverse effect would be very infrequent (96).

A fact that may be relevant is that the different extracts used among women in the whole world, as well as in the communicated cases, are very changeable between themselves, not only in the composition but in the active principles dose as well. The proceeding and the extraction way, as well as the source, determined that mainly. In fact, in a research about phytochemical profile of 11 extracts, high variability between them was found and, in general, lower doses than showed in the label (99). Clinical assays have been executed particularly with a standard isopropanolic extract, with more than 11.000 patients, during a year, with no hepatotoxicity findings.

Recently, an american experts committee developed an exhaustive revision that established in 30 the number of non duplicated cases that have been communicated about liver damage due to CR, concluding that even though the casual relation was possible in all of them, it's not proved in none of them and that it cannot be even estimated as probable (100). In fact, a recent revision about efficacy and security of CR in cancer patients concluded that the security profile of these extracts was quite good and secure even in patients with breast cancer without pathology or risk of liver alterations (101).

In consequence, SMS concludes that it hasn't been detected by the use of CR mutagenic, toxic or carcinogenic actions. The more frequent adverse effects registered in the assays are gastrointestinal (dyspepsia, nausea, vomit), skin reaction, cephalea, vertigo and ataxia or vaginal bleeding, but most of them are slight and self-limited, not leading to treatment interruption. It also points out CR extracts use to releasing climacteric symptomatology at recommended doses is safe from the hepatic perspective. However, it seems to be prudent to avoid it in patients with liver function alterations and to stop it in case symptoms related appear (4).

4.8. Drug obtaining and associations

Current researches about CR are focused in the identification, quality increasement and composition of the vegetal drug and its extracts. Present evidences suggest that treatment efficacy with CR extracts may variate mainly due to dose, administration dosage and manufacturing. Twenty mg every12 hours dose seems to be the most appropriate one, and higher quality evidence have been generated researching about a standard isopropanolic extract of CR.

Biologic and chemical techniques are indispensable, like randomized amplified polymorphic DNA-polimerase chain reaction (RAPD-PCR), for the identification and quality control of the drug (102). Such control must begin in the plant grow, with agricultural good practices, and must finish with the formulation, with the manufacturing good practices, cause extraction proceedings may modify the phytochemical composition and may variate the pharmacological properties (103, 104).

There are evidences showing that the association of CR with other phytomedicines may widen its pharmacologic profile. The association with *Hypericum perforatum* has been evaluated in a double blind, randomized and controlled research with placebo, with 301 women with climacteric symptoms and a pronounced psychological component. It showed how MRS was reduced 50% against 19.6% in control group, and how Hamilton Depression Rating Scale was reduced in a 41,8% in the treated group and 12,7% in placebo group (105).

In this way, an association with lignanes and isoflavones evaluated in a double blind, randomized, controlled with placebo research showed a reduction in acute climacteric symptoms in post menopausal women with 3 months treatment (106). A possible association with isoflavones was researched in a multicentric randomized, double blind and controlled with placebo research in 124 women with at least 5 stifles per day that received supplements with phytoestrogens plus CR or placebo during 12 weeks, with improvement in both groups but without significant differences between them. Conclusion was that soy isoflavones plus CR supplements did not show a significant effect over climacteric symptoms in perimenopausal women (107).

Nowadays there are several investigation lines opened about the CR effect in different areas of human health. For example, about benign hyperplasia and prostate cancer (108, 109).

5. PERSPECTIVES

Practically all the revisions and metaanalysis Publisher to date point at the need of having a great number of researches that join the characteristics dictated by evidence based medicine to obtain a truthful and reliable information about the effect over vasomotor symptoms and other health aspects not only of isoflavones in general, but also of its different components in particular (genistein, daidzein, biochanine, formonetin), of its dose, and to valuate the action in special subgroups of patients with determined characteristics, like equol producers phenotype, and lasting enough to be able to valuate the changes in the studied aspects, obtaining answers to questions not solved yet.

In this way, it's remarkable the number of developing researches that will analyse the effect of the isoflavones and its different components over brain, breast, bone tissue, cardiovascular risk and sexual function, or over certain pathology as prostate cancer, asthma, Alzheimer disease, diabetes, chronic liver failure or migraine among others. Of these phytoestrogens research areas, probably the one that will experiment a higher development in the next years will be the related with bone health and cardiovascular disease. Most of these researches, with design adjusted to better evidence regulation, are in phase II and III, being carried out in United States, Mexico, Brazil, Asia and Europa. With no doubt, next years will be fascinating due to the information report by these researches in theses surfacing health areas and a relation cause-effect between isoflavones consume and benefits in several health areas could be established.

On the other hand, CR, with a less extended use than isoflavones, has offered to date evidence of relieving vasomotor symptoms. Nowadays different researches about CR effect in different human health areas are carried out. Most of the clinic assays developing are adjusted to evidence based medicine regulation and are designed to valuate the effect over menopausal symptoms as anxiety or stifles, cancer and breast security, metabolic syndrome and coronary disease, bone metabolism or toxicity and pharmacokinetics aspects.

With no doubt, phytotherapy expectativas are several. It's left to define aspects as responders and not responders identification, contraindications, pharmacologic interactions and long term effects over different health areas, some of them surfacing. Anyway, in the next years phytotherapy must be a therapeutic option that may help many women to relieve vasomotor symptoms or benefit of other effects for their health, even not considered or treated as an alternative to classic medicine not incompatible with drugs use, but in an integrator attitude of the different options of treatment for health care.

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Abbreviations: SMS: Spanish Menopause Society; BMD: bone mineral density; HT: hormonal therapy; CR: Cimicifuga Racemosa

Key Words: Menopause, Phytotherapy, Isoflavones, Soy, Black Cohosh, Cimicifuga Racemosa, Review

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